mpn Canadian MPN Group Newsletter

Summer 2016 Vol 1. No. 1

Welcome to the first Canadian MPN Group newsletter!

We will be publishing this newsletter quarterly, with information on what's new in MPN care and research. Each issue we will bring together MPN advances and news, and keep you up to date with the work of the Canadian MPN Group. Comments, ideas and suggestions can be sent to info@mpncanada.com

Spotlight – MPN Clinic at Jewish General Hospital, Montreal

Every newsletter we highlight a leading centre for MPN care and research in Canada. In this issue we look at the MPN Clinic at Jewish General Hospital, Montréal.

Left to right: Sabrina Fowlkes RN, Dr. Jaroslav Prchal and Dr. Shireen Sirhan – the team at the MPN clinic at Jewish General Hospital

The MPN clinic at Jewish General Hospital, Montreal, was founded in 2010 by Drs. Shireen Sirhan and Jaroslav Prchal. It is the leading MPN centre in Québec and the first dedicated MPN clinic in Canada. It was established with the generous support of donor Mr. Edward Pascal who continues to support the program. Dr. Sirhan tells us about the work of the MPN clinic at JGH.

What kind of patients do you see?

The MPN clinic, sees approximately 30 new MPN patients per year. We see patients for initial consultations, second opinions, for the benefit of our expertise in resolving diagnostic challenges, and for clinical trials. Though all types of MPN are seen in the clinic, we do see more MF patients because they are the group with the most advanced disease and are more likely to be referred for second opinions and consideration for clinical trials.

What can patients expect from their care at the MPN clinic?

Our patients are followed closely by our team and to enhance the care of our patients we also have a dedicated nurse familiar with MPN treatments and their side effects. In a chronic disease like MPN it is crucial to monitor patients' quality of life. We assess this during a patient's initial visit and whenever there is a change in treatment.

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MPN Clinic... *continued from page 1*

To better manage the increased risk of cardiovascular complications in MPN patients, we are planning to establish links with internal medicine. Our patients can also benefit from the JGH smoking cessation program.

How is the MPN program at JGH contributing to MPN research?

Our research on MPNs aims to improve outcomes for MPN patients through clinical trials and patient registries.

The MPN clinic is part of the Québec Provincial MPN Registry run through the Groupe Québécois de Recherche en LMC-NMP. We collect data on investigations, treatments, complications and quality of life assessments, especially with change of treatment. This will initially help us understand the scope of practice and highlight areas needing improvement. In the future, we're hoping to use the data for epidemiologic research.

What clinical trials are active in JGH?

The MPN clinic at JGH is currently enrolling myelofibrosis patients for trials for imetelstat (NCT02426086), and the triple combination of ruxolitinib, PIM447 and LEE011 (NCT02370706).

JGH is also participating in a trial of momelotinib in anemic or thrombocytopenic patients (NCT02101268) that is no longer enrolling.

Full details of clinical trials across Canada can be found at mpncanada.com

What does being part of the Canadian MPN Group mean for you?

It means we're able to collaborate more closely with other MPN experts in patient care and research, which is vital in a rare disease area such as MPN. We do this through collaborative research, meetings, monthly teleconferences and jointly published articles on MPN.

Referrals
Referrals should be marked "for the attention of Dr Shireen Sirhan"
Referrals accepted from physicians (preferred) and patients.

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Contact: Hematology MPD Clinic
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Biography – Shireen Sirhan MD FRCPC
Dr. Sirhan completed medical school and training in internal medicine, Hematology and Medical Oncology at McGill University. She went on to train in MPNs under the mentorship of Dr. Ayalew Tefferi at the Mayo Clinic and received a masters degree in Clinical Trials from the University of London. She now runs the MPN Clinic at Jewish General Hospital with Dr. Jaroslav Prchal.

Publications by the Canadian MPN Group

Evolving Therapeutic Options for Polycythemia Vera: Perspectives of the Canadian Myeloproliferative Neoplasms Group. Clin Lymphoma Myeloma Leuk. 2015 Dec;15(12):715-27.

The management of patients with PV has recently undergone major developments following identification of the *JAK2V617F* mutation and development of the JAK1/2 inhibitor ruxolitinib. In this paper, we review the changing landscape of PV management, including diagnosis and the role of the *JAK2V617F* mutation, current and investigational therapies, and patient risk assessment.

Meeting updates

European Hematology Association 21st Annual Congress

During the clinical sessions on MPNs the following abstracts were presented.

An update from the European LeukemiaNet on the outcome of 121 pregnancies in patients with PV. Two groups were examined: group 1 in whom the pregnancy preceded the diagnosis of PV and group 2 in whom PV was diagnosed and managed prior to pregnancy. Live births were significantly better (49% vs 77%) for patients in whom the diagnosis of PV was known and appropriate management performed. Maternal major thrombotic complications were similar between the two groups, while bleeding complications were higher in the treated group.

A cohort study based on Swedish registry data showed an increased risk of second malignancies in patients with MPNs highest risk observed was for acute myeloid leukemia (AML) followed by lymphoid malignancies and non-melanoma skin cancers. Risk for other solid tumors was also increased. Therefore, patients with MPNs should undergo age appropriate screening for malignancies and suggestive symptoms should be investigated.

Data from the REPONSE-2 study of ruxolitinib versus best available therapy in patients with PV who are resistant or intolerant to hydroxyurea and without splenomegaly was presented. The drug was well tolerated. The primary end point of hematocrit control was met in 62% of patients on ruxolitinb versus 18.7 % of patients on BAT. Ruxolitinib was also superior in inducing complete hematologic remission (23% versus 5.3%) and in symptom control with complete symptom resolution (50% versus 7.7% of patients).

An analysis of the PT-1 cohort was performed to look at phenotypic differences and treatment responses in molecular subgroups of ET. *CALR*-mutated ET patients presented with lower hemoglobin and WBC levels and higher platelet counts. This analysis confirmed that the majority of venous thrombotic events occurred in the JAK2-mutated subgroup. Surprisingly, *CALR*-mutated ET patients suffered increased rates of myelofibrotic transformation (HR 3.15) compared to the *JAK2*-mutated subgroup, correcting for age and treatment.

Next generation sequencing was performed on 126 PMF patients to determine whether greater mutational complexity may contribute to the differential prognostic impact of phenotypic driver mutations. The findings supported that the prognostic advantage of CALR mutation in PMF is limited to the type1 mutation. However, there was no evidence of greater molecular complexity of type2 *CALR* to explain this finding. Triple-negative MF patients had a larger number of prognostically negative high molecular risk (HMR) mutations, particularly *SRSF2* mutation, which may partially explain their worse prognosis.

The final 5-year efficacy and safety analysis from the COMFORT-1 study comparing ruxolitinb to placebo in patients with MF showed that responses were durable. In addition, median OS was not reached for patients originally randomized to ruxolitinib, whereas it was 200 weeks for patients randomized to placebo, with a hazard ratio of 0.69 (p=0.025). No new safety signals were observed.

A study analyzed the influence of the genotype on the risk of myeloid transformation in patients with PV and ET. In multivariate analysis, an increased risk of AML/MDS transformation was observed for patients older than 60 years (HR 4.3) with leukocytes >$10x10^9$/L (HR 2.2) and those treated with hydroxyurea plus leukemogenic agents (HR 2.5). Abnormal karyotype was associated with increased risk of transformation in PV (HR 5.1) but not in ET. MPL mutation was an independent risk factor for AML/MDS (HR 6.1). in ET patients.

An exploratory analysis of the RESPONSE trial evaluated the effect of ruxolitinib on the *JAK2* allele burden in PV. At 32 weeks prior to cross over the mean percentage change in baseline *JAK2* allele burden was -12.2% in the ruxolitinib arm and +1.2% in the BAT arm. At the time of the analysis the average maximal reductions in allele burden in ruxolitinib randomized and ruxolitinib crossover arms were -35.9% and -21.2%. A molecular response was not dependent on when in the disease course ruxolitinib was initiated.

A study of mutant CALR, its oncogenic property and molecular mechanism of its activity in a thrombopoietin (TPO)-dependent human megakaryocytic cell line. Expression of mutant but not wild type CALR induced TPO-independent growth and this required c-MPL. Mutant CALR preferentially associated with c-MPL bound to JAK2 over the wild type protein. The mutant-specific C-terminus of CALR interfered with the P-domain of CALR to allow the N-domain interaction with c-MPL, possibly explaning mutant *CALR* gain-of-function. Mutant *CALR* induced JAK2 and downstream. These findings imply that mutant *CALR* activates the JAK2 downstream pathway via its association with c-MPL.

MPN e-SIMPLE App

MPN eSIMPLE
electronic Support to Improve Management through Protocol and Evidence

We are pleased to announce the new MPN e-SIMPLE app, developed with the support of Novartis. The app provides data, resources, and guidance to assist Canadian physicians in daily management of MPNs. The goal is to improve the management of MPNs across Canada by providing point-of-care guidance to our colleagues on therapeutic approaches for each MPN patient.

The app includes disease risk calculators (IPSS, DIPSS, DIPSS Plus and IPVS), resources for MPN diagnosis and risk assessment, and information on treatment options. At present the app covers MF and PV, with ET coming soon.

MPN e-SIMPLE can be used using your web browser or downloaded (Android & iOS, optimized for tablets) at **www.mpnesimple.ca**

Clinical trials update

A full list of clinical trials in Canada and contact details for MPN centres can be found on our website.

Currently enrolling for MF

PRM-151 [NCT01981850] – This phase 2 study is investigating PRM-151 safety in MF patients, and whether the drug has an effect on fibrosis. Eligibility criteria include intermediate-1/2 or high risk MF and patients cannot be a candidate for ruxolitinib. Currently enrolling: Princess Margaret Cancer Centre (Toronto), Providence Hematology (Vancouver).

PIM447 [NCT02370706] – This study is examining the safety of double and triple drug combinations of PIM447 (PIM inhibitor), ruxolitinib and LEE011 (CDK inhibitor). Eligibility criteria include *JAK2V617F* positive MF. Different arms of the trial accept ruxolitnib naïve, responsive, relapsed, and refractory patients. Currently enrolling: Princess Margaret Cancer Centre (Toronto).

Ruxolitinib in high-risk MF [NCT02598297] – This study is evaluating the use of ruxolitinib in high molecular risk (HMR) early MF patients. Eligible patients must have ≥1 mutation in one of the five HMR genes (ASXL1, EZH2, SRSF2 and IDH1/2), at least grade 1 fibrosis and be JAK1/2 inhibitor naïve. Currently enrolling: Princess Margaret Cancer Centre (Toronto).

Imetelstat in MF [NCT02426086] – This study is evaluating two dose levels of imetelstat in intermediate-2/high risk MF patients previously treated with a JAK1/2 inhibitor. Eligible patients must be relapsed/refractory to JAK1/2 inhibitor treatment. Currently enrolling: Jewish General Hospital (Montreal).

Currently enrolling for SM, PED, MF and CMML

SL-401 in advanced high-risk MPNs [NCT02268253] – This study is evaluating the safety of SL-401 in patients with high-risk MPNs (systemic mastocytosis [SM], advanced symptomatic hypereosinoophic disorder [PED], myelofibrosis [MF], and chronic myelomonocytic leukemia [CMML]). Currently enrolling: Princess Margaret Cancer Centre(Toronto).

The Canadian MPN Group

The Canadian MPN Group relies on donor contributions to pursue our mission of improving the care and research in patients with myeloproliferative neoplasms.

How to help - you can donate through our website at www.mpncanada.com. For more information on how you can support the Canadian MPN Group, please contact info@mpncanada.com

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For further information, please contact info@mpncanada.com

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